Personalized DNA neoantigen vaccine in combination with plasmid IL-12 and pembrolizumab for the treatment of patients with advanced hepatocellular carcinoma

Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death. Immune checkpoint inhibitors targeting PD-1 have limited activity in HCC as monotherapy, with response rates ranging from 14-17%. Tumor neoantigens derived from tumor-specific mutations can be incorporated into personalized therapeutic cancer vaccines to prime T cell responses, potentially enhancing responses to anti-PD1 therapy. DNA vaccines have been shown to elicit strong CD8 and CD4 T cell responses in preclinical and clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. GNOS-PV02 is a personalized DNA vaccine, encoding up to 40 patient-specific neoantigens. In the GT-30 trial, it is used in combination with INO-9012 (plasmid-encoded IL-12) and pembrolizumab for the treatment of advanced HCC.

Methods: The GT-30 trial (NCT04251117) is a single-arm phase I/II clinical trial to assess the safety, immunogenicity, and preliminary efficacy of GNOS-PV02 in combination with INO-9012 and pembrolizumab in patients with advanced HCC. Twenty-four patients are anticipated to be enrolled. Patients are recruited upon diagnosis or during first-line treatment with tyrosine kinase inhibitors (TKI). Tumors are biopsied for exome and transcriptome sequencing. The tumor specific vaccine is designed, optimized and manufactured during first-line therapy. Each vaccine encodes up to 40 neoantigens, which includes all detected neoantigens for the majority of HCC patients. After progression or intolerance with first-line therapy, patients can commence trial therapy with concurrent personalized vaccine and pembrolizumab. GNOS-PV02 + INO-9012 are administered Q3w for the first 4 doses and Q9w thereafter until disease progression. Pembrolizumab is delivered Q3w until disease progression. Immunogenicity of each of the vaccine epitopes will be determined by ex vivo ELISpot and flow cytometry. Clinical activity is assessed by RECIST1.1 at baseline and every 9 weeks. Serial biopsies will be obtained at 9 weeks and upon disease progression to evaluate changes in the exome, transcriptome and changes to the tumor microenvironment.

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